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DOI:

[10.1016/j.biopsych.2016.05.024](https://doi.org/10.1016/j.biopsych.2016.05.024)

Document Version

Peer reviewed version

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Citation for published version (APA):

Verduijn, J., Milaneschi, Y., Peyrot, W. J., Jan Hottenga, J., Abdellaoui, A., de Geus, E. J. C., Smit, J. H., Breen, G., Lewis, C. M., Boomsma, D. I., Beekman, A. T. F., & Penninx, B. W. J. H. (2016). Using clinical characteristics to identify which patients with major depressive disorder have a higher genetic load for three psychiatric disorders. *Biological psychiatry*. <https://doi.org/10.1016/j.biopsych.2016.05.024>

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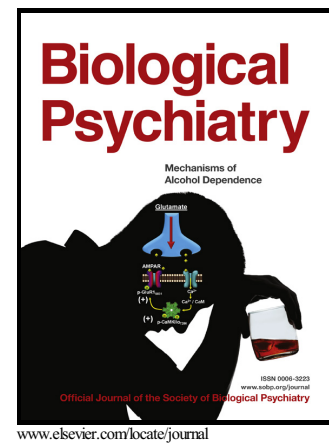
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PII: S0006-3223(16)32469-6
DOI: <http://dx.doi.org/10.1016/j.biopsych.2016.05.024>
Reference: BPS12906

To appear in: *Biological Psychiatry*

Received date: 26 October 2015
Revised date: 2 May 2016
Accepted date: 24 May 2016

Cite this article as: Judith Verduijn, Yuri Milaneschi, Wouter J. Peyrot, Jouke Jan Hottenga, Abdel Abdellaoui, Eco J.C. de Geus, Johannes H. Smit, Gerome Breen, Cathryn M. Lewis, Dorret I. Boomsma, Aartjan T.F. Beekman and Brenda W.J.H. Penninx, Using clinical characteristics to identify which patients with major depressive disorder have a higher genetic load for three psychiatric disordersIncreased genetic load in MDD characteristics subgroups, *Biological Psychiatry*, <http://dx.doi.org/10.1016/j.biopsych.2016.05.024>

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Using clinical characteristics to identify which patients with major depressive disorder have a higher genetic load for three psychiatric disorders.

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Running head: Increased genetic load in MDD characteristics subgroups

Keywords: Major depressive disorder, heterogeneity, genetics, genetic load, clinical characteristics, staging, replication

ABSTRACT

Background: Limited successes of gene finding for Major Depressive Disorder (MDD) may be partly due to phenotypic heterogeneity. We tested whether the genetic load for MDD, bipolar disorder (BIP), and schizophrenia (SCZ) is increased in phenotypically more homogenous MDD patients identified by specific clinical characteristics.

Methods: Patients (n=1539) with a DSM-IV MDD diagnosis and controls (n=1792) were from two large (NESDA and NTR) cohort studies. Genomic profile risk scores (GPRS) for MDD, BIP and SCZ were based on meta-analyses results of the Psychiatric Genomics Consortium. Regression analyses (adjusted for year of birth, gender, three principal components) examined the association between GPRS with characteristics and with MDD subgroups stratified according to the most relevant characteristics. The proportion of liability variance explained by GPRS for each MDD subgroup was estimated.

Result: GPRS-MDD explained 1.0% ($p=4.19e^{-09}$) of MDD variance, and 1.5% ($p=4.23e^{-09}$) for MDD endorsing 9 DSM symptoms. GPRS-BIP explained 0.6% ($p=2.97e^{-05}$) of MDD variance and 1.1% ($p=1.30e^{-05}$) for MDD with age at onset <18 years. GPRS-SCZ explained 2.0% ($p=6.15e^{-16}$) of MDD variance, 2.6% ($p=2.88e^{-10}$) for MDD with higher symptom severity, and 2.3% ($p=2.26e^{-13}$) for MDD endorsing 9 DSM symptoms. An independent sample replicated the same pattern of stronger associations between cases with more DSM symptoms, as compared to overall MDD, and GPRS-SCZ.

Conclusion: MDD patients with early age at onset and higher symptom severity have an increased genetic risk for three major psychiatric disorders, suggesting that it is useful to create phenotypically more homogenous groups when searching for genes associated with MDD.

INTRODUCTION

Major depressive disorder (MDD) has long been recognized to be heritable (~37%,⁽¹⁾). However, today, the largest genome-wide association study (GWAS) in MDD by the Psychiatric Genomics Consortium (PGC) has failed to find significant associations with single genetic variants (SNPs).⁽²⁾ One likely reason why it failed is that current available sample sizes are underpowered to detect small genetic effects;⁽³⁾ studies have shown that a large proportion of MDD liability is due to joint polygenic effect of common SNPs with small effects scattered across the genome and shared with other psychiatric disorders such as bipolar disorder (BIP) and schizophrenia (SCZ).^(3;4) A second reason may be MDD's clinical heterogeneity: various patients with the same diagnosis will have experienced a differential illness course with variation in e.g. experienced number-, duration-, and severity of episodes.⁽⁵⁾ It has therefore been suggested that GWAS studies should be done in phenotypically more homogenous MDD patients.^(2;3) The Converge Consortium showed this by examining recurrent MDD cases in Chinese women.⁽⁶⁾ However, there might be other characteristics that could be selected to enhance the genetic signal. Based on family studies^(7;8) it has been suggested that the highest genetic load will be found in the most severe MDD phenotype, e.g. patients with young age at onset, longer (chronic) duration-, higher severity of symptoms, and recurrent episodes.^(1;9;10) Moreover, clinical staging strategies using jointly different clinical characteristics to define stages of MDD progression^(11–13) may also be applied.

To our knowledge it has been barely examined whether genome-wide genomic profile risk scores (GPRS) are associated with clinical depression characteristics that indicate a more severe MDD phenotype. One study in depression suggests that a higher GPRS increases an individual's susceptibility for experiencing chronically high levels of depressive symptoms.⁽¹⁴⁾

The current study will examine whether the genetic risk for MDD, BIP and SCZ estimated using GPRS generated from PGC meta-analysis results(2;15;16), is increased in phenotypically more homogenous MDD subgroups of patients stratified by clinical characteristics reflecting a more severe MDD phenotype (younger age at onset, longer duration of depressive symptoms, positive MDD family history, more DSM symptoms, higher severity of depressive symptoms, and the presence of recurring MDD episodes). In addition to single characteristics, we additionally stratify patients according to an established MDD clinical staging model reflecting MDD progression.(12;13) Finally, we aim to replicate main findings in an independent dataset.(17)

MATERIALS & METHODS

Sample

The sample consisted of 3331 unrelated participants (median year of birth 1967, range 1926-1994) of North-European ancestry from the Netherlands Study of Depression and Anxiety (NESDA) (n=1851) and from the Netherlands Twin Register (NTR) (n=1480). The methodology of both NESDA and NTR and their biobank projects have been extensively described elsewhere.(18–20) The genetic sample selection is identical to the one used by Milaneschi et al.(21)

In short, NESDA is an ongoing longitudinal study into the onset and course of depressive and anxiety disorders. At baseline (2004-2006) 2981 adults between the age of 18 and 65 were recruited from community (19%), general practice (54%) and specialized mental health care (27%) to represent the entire developmental spectrum of both disorders, including healthy controls. After baseline, 2, 4 and 6-year follow-up assessments have been performed.

NTR has collected longitudinal data on Dutch twin families involving nearly 40,000 adult

participants. The ethical review boards of contributing universities approved both studies and all participants signed informed consent.

MDD diagnoses.

The present study consisted of 1539 cases with a lifetime diagnoses of MDD (history of an MDD episode during any of their interviews) and 1792 controls. All cases were drawn from NESDA.

The presence of MDD was assessed with the DSM-IV Composite International Diagnostic Interview (CIDI) version 2.1.(22) administered by specially trained research staff at baseline or one of the biannual follow-up assessments. From NESDA, we selected healthy controls (n=312), participants without lifetime MDD or anxiety disorder.

From NTR, the majority of controls (n=1480) were drawn, participants who had no report of MDD, a low factor score based on a multivariate analyses of depressive complaints, anxiety, neuroticism and somatic anxiety.(23;24)

Clinical characteristics.

For MDD cases (all from NESDA) several clinical characteristics were assessed. Age at onset was ascertained via CIDI interview. Duration of depressive symptoms was examined with the Life-Chart,(25) and expressed as the percentage of ~10 years (~4 years before baseline + ~6 years of follow-up) spent with depressive symptoms. Presence of a first-degree family (no/yes) member with depression was assessed with the family-tree method.(26) Two different measures indexed depression severity: the highest number of DSM symptoms ever endorsed during an MDD episode extracted from the CIDI (range 5-9), and the average score on 4 measures (at each assessment) of the inventory of depressive symptom (IDS).(27) Recurring MDD episodes (yes/no) was extracted from the CIDI. Finally, we applied a clinical staging algorithm(12;13;28)

(supplement-page 6, eFigure1), combining different clinical characteristics. Cases were assigned to three stages: stage 2 (n=303) first episode; stage 3 (n=631) recurrent/relapse episode; stage 4 (n=605) chronic, an episode lasting longer than 2 years as indicated by the CIDI at baseline, or the life-chart during follow-up.

Genotyping and genetic relationship matrix

Blood sample collection and DNA extraction methods have been previously described.(18) Autosomal SNPs were genotyped on the Affymetrix 6.0 Human Genome-Wide SNP Array in three separate batches. Quality control (QC) steps have been previously described.(29;30) Primary analyses included 497,347 SNPs. Additional stringent QC was performed to build a genetic-relationship-matrix (GRM) to reduce the possibility that estimates from GRM-based analyses could be inflated by artifacts. The remaining 435,579 SNPs were used to build the GRM using GCTAv.1.24.1(31) Supplement-page 3 describes QC steps.

Genomic profile risk scores (GPRS)

As previously described(21) (more detail in supplement-page 3), results from the PGC were used to derive GPRS for MDD(2), BIP(15), and SCZ(16). Eight sets of scores alleles were selected based on significance thresholds ($P < .0001$, $< .001$, $< .005$, $< .01$, $< .05$, $< .1$, $< .5$, < 1) of the discovery samples associations. GPRS were calculated as the number of scores alleles weighted by effect sizes (log-OR) from the discovery statistics (number of SNPs included for each P_t see supplement-eTable 2). GPRS construction method based on LD pruning and P-thresholding may limit their predicting accuracy by discarding information on LD structure.(32) Additionally, we derived GPRS using the LDpred approach using LD information from a reference panel.(32) Both

GPRS thresholds and LDpred were standardized to a mean of zero and standard deviation of one to aid interpretation of results.

Statistical analyses

Differences in demographics between MDD cases and controls were examined using Mann-Whitney u-tests for continuous and chi-square test for categorical variables.

Firstly, focusing on MDD cases (n=1539) we regressed genetic risk (GPRS-thresholds and LDpred) over clinical characteristics of MDD (age at onset, duration of symptoms, family history, number of DSM symptoms, severity of symptoms, recurring episodes, stages) using linear regression analyses. In order to discard spurious correlations we applied a strategy combining permutation-based empirical p-values GPRS of the same characteristics and false discovery rate across main clinical characteristics for each GPRS (see supplement-page 4). Only the GPRS-characteristic pairs showing the most consistent (higher number of significant tests across GPRS) profile of associations were selected for further analyses.

Thus, MDD cases were stratified in subgroups of similar dimensions (based on distribution quantiles for continuous characteristics) according to each clinical characteristic selected in the previous step. The associations between GPRS and MDD (subgroups) were estimated with (multivariate) logistic regressions with controls as reference.

Next, the proportion of variance explained by GPRS on the liability scale for MDD (subgroups) was estimated using the R^2 coefficient proposed by Lee et al.,(33) which is directly comparable with heritability and robust against ascertainment bias. Linear transformation on the liability scale was based on prevalence (K) of 0.18 for MDD (Dutch lifetime prevalence;(34) Ks for subgroups were empirically derived by dividing the prevalence for MDD by the number of subgroups.

Finally, the total variance in liability explained by the joint effect of all SNPs (SNP-heritability, h^2 SNP) for specific subsets of MDD selected according to clinical characteristics was estimated using genomic-relationship-matrix restricted maximum likelihood (GREML) analyses.(35) The h^2 SNP is estimated in a linear mixed model in which the measure of genetic similarity (based on the GRM) is included as a random effect to predict the phenotype. Furthermore, the genetic covariance (COV) between specific subsets of MDD selected according to clinical characteristics and the traits on which the risk scores were trained was estimated using the AVENGEME package(36) utilizing the results from GPRS analyses (applied settings in supplement-eTable 4).

All analyses were adjusted for year of birth, gender, and three ancestry informative principal components to take possible population stratification into account.(30) Analyses, were performed with SPSS (v. 20.0, IBMcorp, 2011), R (v. 3.2.3, R Project for Statistical Computing) and GCTAv.1.24.1.(31) Nominal significance was set at $p < 0.05$, using two-tailed tests.

Replication sample

One main finding was replicated in RADIANT-UK an independent cohort(37), from which we selected 1602 cases with a lifetime MDD diagnosis and 1390 controls who screened for absence of any psychiatric disorder. MDD presence was assessed with the schedules for clinical assessment in neuropsychiatry (SCAN) interview.(38)

Imputed (HapMap3) genotype data of RADIANT-UK were processed according to QC steps described in detail in a previous publication by our group.(39) GPRS-SCZ were prepared on 76,201 independent SNPs (see supplement-page 5, eTable 6).

RADIANT-UK analyses were adjusted for age at interview, gender, and ten principal components.(17)

RESULTS

Cases (n=1539) were older, and more often female than controls (n=1792), see Table 1. Of cases, 70.5% had recurrent episodes. Chronic episodes (stage 4, lasting longer than two years), were experienced by 33% of those with a first and >40% of those with a recurrent episode.

Clinical characteristics and GPRS

Within the MDD cases (n=1539), the regression analyses showed consistent patterns of associations for five GPRS-characteristic relationships (supplement-eTable 1): high GPRS-MDD with increased number of DSM symptoms (4 significant, 3 of which with FDR $q < 0.10$; top: $Pt < .05$, $\beta .063$, SE .026, empirical $P\text{-value} = .014$), high GPRS-BIP with earlier age at onset (5 significant, 3 of which with FDR $q < 0.10$; top: $Pt < .005$, $\beta -.115$, SE .031, empirical $P\text{-value} = 2e^{-04}$), and high GPRS-SCZ with higher IDS scores (5 significant, 4 of which with FDR $q < 0.10$; top: $Pt < .01$, $\beta .089$, SE .025, empirical $P\text{-value} = 3.74e^{-04}$). Both high GPRS-BIP and high GPRS-SCZ were also associated with number of DSM symptoms (GPRS-BIP 3 significant, 1 of which with FDR $q < 0.10$; top: $Pt < 0.05$, $\beta .065$, SE .026, empirical $P\text{-value} = .012$; GPRS-SCZ 3 significant, 2 of which with FDR $q < 0.10$; top: LDpred, $\beta .064$, SE .026, empirical $P\text{-value} = .013$). These five GPRS-characteristic pairs were carried forward in subsequent analyses.

Family history, duration of symptoms, recurring episodes, and MDD stages showed no consistent associations with GPRS.

Subgroup analyses

MDD cases were stratified in subgroups of approximately similar dimensions according to age at onset quartiles (Q1 >37 years (n=392), Q2 26-37 years (n=380), Q3 18-25 years (n=398), Q4 <18

years (n=360)), number of DSM symptoms (DSM5/6 (n=244), DSM7 (n=302), DSM8 (n=442), DSM9 (n=499)) and IDS scores quartiles (IDS<13 (n=384), IDS 13-20.25 (n=385), >20.25-29 (n=387), and IDS>29 (n=377)).

Figure 1 depicts the proportion of variance explained by GPRS on the liability scale for MDD (subgroups); p-values are from (multinomial) logistic regression (full results in supplement-Table 3). GPRS-MDD, explained maximal 1.0% of liability variance for overall MDD, and 1.5% for MDD endorsing 9 DSM symptoms. GPRS-BIP explained maximal 0.6% for overall MDD, 1.1% for MDD with age at onset <18 years, and 0.7% for MDD endorsing 9 DSM symptoms. GPRS-SCZ explained maximal 2.0% for overall MDD, 2.6% for MDD with IDS score >29, and 2.3% for MDD endorsing 9 DSM symptoms.

Analyses were repeated collapsing the 2 subgroups with the highest explained variance for each characteristic: GPRS-MDD explained maximal 1.1% of liability variance for MDD endorsing ≥ 8 DSM symptoms (DSM-high, n=941); GPRS-BIP maximal 0.8% for MDD with an onset <26 years (AaO-young, n=758), and maximal 0.9% for DSM-high; and GPRS-SCZ maximal 2.7% for MDD with IDS scores >20.25 (IDS-high, n=764) and 2.2% for MDD DSM-high.

Previous analyses were repeated after the inclusion of 590 controls selected with less stringent criteria (see supplement-page 5): results were unchanged suggesting that different selection criteria for controls do not impact on the association with GPRS.

SNP-heritability of MDD subgroups and Genetic Covariance with psychiatric traits.

We estimated h^2 SNP for the subgroups of MDD AaO-young, DSM-high and IDS-high, allowing us to focus on approximately half of the cases. SNP-heritability could not be reliably estimated for AaO-young ($K=0.09$; $est=.208$, $se=0.15$, $p=7.95e^{-2}$). This may suggest that the drop in (half)

sample size was not balanced by an increased genetic homogeneity of this subgroup. Indeed, considering the results depicted in Figure 1, an increased genetic signal may be expected especially at very early age at onset, which would not allow us to retain a substantial sample size for GREML analyses. GREML analyses showed that h^2_{SNP} estimates were 0.44 for DSM-high ($K=0.12$; $se=0.14$, $p=8.24e^{-4}$), and 0.48 for IDS-high ($K=0.09$; $se=0.15$, $p=5.52e^{-4}$), although all with large standard errors due to restricted sample sizes. Estimates for DSM-high and IDS-high were suggestively higher than the estimate for MDD-overall previously reported in same sample (estimate=0.31; $se=0.13$; $p=0.006$)(21), although with overlapping confidence boundaries. The genetic covariance with bipolar disorder was 0.16 (95%CI, 0.11-0.22) when focusing on cases with AaO-young. The genetic covariance with schizophrenia was 0.11 (95% CI 0.09-0.13) when focusing on cases with IDS-high, and 0.12 (95%CI, 0.10-0.14) in cases with DSM-high.

Replication: GPRS-SCZ and MDD with high number of DSM symptoms.

We used RADIANT-UK to replicate our finding on increased GPRS-SCZ in cases with a high number of DSM symptoms (DSM-high, endorsing 8-9 symptoms). We selected this association as benchmark for several reasons: (i) DSM symptoms were available in both cohorts (IDS only in NESDA) and had a similar distribution (see supplement-eFigure 4); (ii) GPRS-SCZ explained a higher proportion of liability variance for DSM-high than GPRS-MDD (Figure 1); (iii) RADIANT-UK had no overlapping samples with PGC-SCZ discovery(16), while shared samples with PGC-MDD and PGC-BIP discovery sets.(2;15) The association between GPRS-BIP and young MDD onset is replicated in an under review PGC paper based on all the contributing cohorts (including NESDA and RADIANT-UK) and therefore was not considered further here.

Polygenic scores analyses in NESDA predicting DSM-high (941 cases versus 1792 controls) had $\geq 80\%$ power (estimated using the AVENGEME package(36), parameter settings in

supplement-eTable 5) to detect a significant ($\alpha=0.05$) association for GPRS-SCZ with Pts equal/higher than <0.01 , with an expected R^2 range of 0.3-1.8%. In RADIANT-UK, the power to detect the same significant association with 878 cases and 1390 controls was $\geq 80\%$ for GPRS-SCZ with Pts equal/higher than <0.05 , with an expected R^2 range of 0.8-1.4% (parameter settings in supplement-eTable 8).

RADIANT-UK cases ($n=1602$) were older (mean=46.4yrs) than controls ($n=1390$) (mean=41.8yrs), and more often female (70.6% vs. 60.2%). 1462 cases had information on the number of DSM symptoms (median 8.00 range 5-9) experienced. GPRS-SCZ, explained maximal 0.9% of liability variance for overall MDD, and 1.1% for DSM-high ($n=878$) (Figure 2, supplement-eTable 7).

Pooled data-analyses, of the odds ratios derived from logistic regression analyses comparing the GPRS-SCZ in MDD overall versus controls and in MDD DSM-high versus controls both in NESDA and RADIANT-UK, showed that the odds for DSM-high versus controls were higher than the odds for MDD overall versus (Figure 3, supplement-eTable 9).

DISCUSSION

The current study examined whether the genetic risk for MDD, bipolar, and schizophrenia is increased in phenotypically more homogenous MDD subgroups of patients stratified by clinical characteristics reflecting a more severe MDD phenotype and stratified by clinical MDD stages reflecting progression of MDD. The present findings showed that MDD cases with a younger age at onset have a higher genetic load for bipolar disorder, and those with severe depression, as indexed by repeated measure of depressive symptoms, had higher genetic risk for schizophrenia. Moreover, cases with a high number of endorsed DSM symptoms showed also higher genetic risk for all major psychiatric disorders considered.

Differential association between polygenic scores for different psychiatric disorders and MDD specific clinical characteristics indicate that these features may be able to identify specific subgroups of depressed patients genetically more similar to the discovery traits. Indeed, polygenic score for bipolar explained 0.6% of liability variance for MDD and 1.1% when focusing on cases with early age at onset. Similarly, polygenic score for schizophrenia explained 2.0% of liability variance for MDD and 2.7% when focusing on cases with high symptoms severity. Association of polygenic scores of a trait (e.g. GPRS-MDD) on subgroups of the same trait (e.g. MDD characteristic groups) is often more difficult to interpret, especially when the index characteristics and its distribution are unknown in the discovery data.⁽³⁵⁾ However, in this case some interpretation is more plausible, as the number of DSM symptoms, associated with polygenic score of MDD, may clearly represent a proxy for disease severity. A further noticeable finding is that GPRS-SCZ scores explained the highest proportion of variance in MDD liability, higher than GPRS-MDD scores. This higher explanatory power is attributable to the larger training set for GPRS-schizophrenia⁽⁴⁰⁾, in a previous paper we calculated that if we would have the same size of training set for depression GPRS-MDD as used for GPRS-SCZ, we would have at least similar variance explained.⁽²¹⁾

The hypothesis that phenotypical more homogenous MDD cases as stratified by characteristics reflecting a more severe MDD phenotype (young age at onset, recurrent, chronic) have an increased genetic load is among other things based on the finding that some characteristics predict a familial risk on major depression. The risk of depression has consistently shown to be higher in family members of probands with early-onset recurrent MDD than family members of late-onset single episode.^(1; 7) Our finding that GPRS-BIP is significantly higher in a young onset versus later onset MDD could suggest that patients with an early onset of depression may have a higher genetic risk to develop bipolar disorder later in life. This is in line

with literature showing that the age at onset for bipolar disorder is generally younger than the age at onset for MDD(7), and that an early age at depression onset is a risk factor for developing bipolar disorder later on.(41–43) One other study on MDD patients showed that early age at onset (<18 years) was associated with a higher genetic bipolar load.(44) Besides age at onset, we found that higher number of DSM symptoms and higher severity of depressive symptoms are also associated with an increased genetic risk, especially GPRS-SCZ. It could be that a higher genetic risk for schizophrenia might cause more severe MDD. It is known that severe forms of MDD often presents itself with psychotic symptoms.(45;46) To our knowledge one other study has examined the association between depression severity and genetic load, and found that the mean number of depressive symptoms was associated with genetic risk.(14) This study, however, only included older adults (>50yrs), GPRS were based on same trait examined, and no official depression diagnosis was made. In a larger sample than the current one, it would be interesting to examine whether this association between high number/severity of symptoms and increased genetic schizophrenic risk is driven by specific symptoms that are particularly relevant to psychosis.

We found no associations between genetic load and duration of symptoms, family history of depression, recurring MDD episodes, and MDD stage. An explanation for our negative results on family history and GPRS could be that family history is important for the onset of MDD, but in persons with MDD a higher genetic load exists regardless of their family history. In addition, our measurement of family history may not have been very sensitive to distinguish only the most severe family cases, as reported family history was quite high. Finally, familial aggregation may be considered a rather broad index for genetic risk (which may include also the effect of all kinds of genetic influences and the shared environment). In the current study we used GPRS, which rely only on the additive effect of common variants, while we considered only

the additive genetic risk arising from common variants. A reason why we did not find a genetic load difference between first and recurrent episodes may be that those with a first episode will develop a recurrent episode in the future and therefore will be phenotypically the same as those that have already a recurrent episode. In addition, quite a large proportion of our first episode patients had already a chronic episode. Finally, there was no significant difference in genetic load across the staging model of MDD either (see supplement-page 6).

Overall, the present results suggest that subgroups of MDD patients selected according to specific clinical characteristics may be genetically more homogenous. For instance, estimates of the proportions of variance explained by common genetic variants on the liability for MDD cases with severe symptoms (48%) and high number of endorsed DSM symptoms (44%) were suggestively higher than the estimate obtained for overall MDD in the same sample (31%).⁽²¹⁾ Nevertheless, these results require replication in larger samples, as the limited sample size determined substantial uncertainty around the estimates. These genetically more homogenous sub-phenotypes could be applied to large gene-discovery studies in order to boost the power to detect variants associated to MDD. However, detailed data on the clinical characteristics may not be available in all cohorts participating in large collaborative genetic studies. In this case a simpler strategy based on data likely available in the majority of studies may still represent a viable option to harmonize sub-phenotypes across cohorts. In the present study MDD with severe symptoms (as indexed by repeated measures of the Inventory of Depressive Symptoms) showed the highest SNP-heritability, and therefore may have represented the best potential candidate sub-phenotype. However, not all MDD genetic studies necessarily include longitudinal measurements by the same scale. In replication analyses in RADIANT-UK, not including IDS assessments, we focused on the available data of the number of endorsed DSM symptoms. RADIANT-UK showed the same pattern of a stronger association, as compared to overall MDD,

between cases with high number of DSM symptoms and genetic risk score for schizophrenia. Our results showed that selection of cases with an early age at onset might represent another option to stratify MDD patients. This is underlined by the findings of a study based on the larger PGC-MDD data pool which found that GPRS-BIP is associated with an earlier age at MDD onset.(47)

Our results suggest that focusing on phenotypically more homogenous MDD subgroups of patients as stratified according to characteristics reflecting a more severe MDD phenotype, might be a solution to find SNPs/genes associated with MDD. This was recently supported by a GWAS that found two genetic-loci significantly contributing to the risk of MDD in a homogenous subgroup of Chinese women with recurrent MDD.(6) Besides standard clinical characteristics (recurrence, age at onset) to create phenotypically more homogenous MDD subgroups that are genetically more identical, there is evidence that subgroups based on symptom subtype (melancholic versus atypical MDD)(21) or postpartum depression(48) might also be a possibility to identify genetic more homogenous MDD groups. Moreover, it could be useful to focus on subgroups exposed to a certain environmental factor when studying the genetic effect on MDD.(29)

The core strengths of our study are the large number of participants with available genetic data, well-characterized in terms of clinical MDD characteristics, representing different developmental stages of MDD. Moreover, we used GPRS based on large international consortia and we additionally built GPRS with the new LDpred approach, which is suggested to increase predictive accuracy above commonly used methods for GPRS.(32)

In conclusion, the present study showed that the genetic risk for three major psychiatric disorders is increased in persons with phenotypically more homogenous MDD according to characteristics reflecting a more severe MDD phenotype. Our results showed that MDD patients

with an early age at onset, high number of DSM symptoms, and moderate to severe symptoms across years have the highest genetic risk. Our results suggest that in genetic studies for depression, in conjunction with a continuous effort in increasing sample sizes, it may be useful to create more homogenous subgroups based on those phenotypical characteristics in search for genes associated with MDD.

ACKNOWLEDGEMENTS.

NESDA

The Netherlands Study of Depression and Anxiety and the Netherlands Twin Register: funding was obtained from the Netherlands Organization for Scientific Research (NWO) and MagW/ZonMW grants Middelgroot-911- 09-032, Spinozapremie 56-464-14192, Center for Medical Systems Biology (CSMB, NWO Genomics), Genetic influences on stability and change in psychopathology from childhood to young adulthood (ZonMW 912-10-020), NBIC/BioAssist/RK (2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI–NL, 184.021.007), VU University's Institute for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam (NCA); the European Science Council (ERC Advanced, 230374).

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Centre, GGZ inGeest, Arkin, Leiden University Medical Centre, GGZ Rivierduinen, University Medical Centre Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Institute for Quality of Health Care (IQ Healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos)).

Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health, Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the Avera Institute, Sioux Falls, South Dakota (USA) and the National Institutes of Health (NIH R01 HD042157-01A1, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Computing was supported by BiG Grid, the Dutch e- Science Grid, which is financially supported by NWO. We are grateful to the Psychiatric Genomics Consortium (MDD group) for providing the summary statistics for meta-analyses of MDD, BIP and SCZ after removal of the Dutch GWAS cohort.

RADIANT-UK

Genotyping of the UK RADIANT study was supported by the U.K. Medical Research Council (G0701420). This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

FINANCIAL DISCLOSURES

All other authors report no biomedical financial interests or potential conflicts of interest.

Supplemental material is available at the journal website.

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TABLE & FIGURES LEGENDS

Table 1. Descriptives of controls and MDD cases (n=3331), characteristics of MDD cases (n=1539).

Figure 1: NESDA, % explained variance for MDD status (All MDD cases or those with DSM-high/ISD-high/AaO-young) versus controls

Explained variance assuming a liability threshold model and $K=0.18$ (MDD), $K=0.18/4$ (DSM, IDS and AaO quartiles), $K=0.18/2$ (DSM-high, IDS-high, AaO-young)

P-values from binary (MDDall, DSM-high, IDS-high, AaO-young) and multinomial (subgroups) logistic regression (reference=controls, n=1792); adjusted for year of birth, gender and 3 principal components

Figure 2: RADIANT-UK, % explained variance for MDD status (All MDD cases or those with DSM-high) versus controls

Explained variance assuming a liability threshold model and $K=0.18$ (MDD), $K=0.18/2$ (DSM-high)

P-values from binary (MDDall, DSM-high) logistic regression (reference=controls, n=1390); adjusted for age, gender and 10 principal components

Figure 3: NESDA, RADIANT-UK, POOLED, comparing odds ratios of MDD all cases versus DSM-high cases, reference are controls.

A: NESDA MDD CASES (n=1539) vs. MDD CASES DSM symptoms high (n=941), reference controls (n=1792)

B: RADIANT-UK MDD CASES (n=1602) vs. MDD CASES DSM symptoms high (n=878), reference controls (n=1390)

C: POOLED NESDA and RADIANT-UK, MDD CASES (n=3141) vs. MDD CASES DSM symptoms high (n=1819), controls (n=3182)

Table 1. Descriptives of controls and MDD cases (n=3331), characteristics of MDD cases (n=1539).

	No MDD n=1792	MDD n=1539
Demographics		
Year of Birth, Med (IQR) ^a	1972 (1958–1979)	1962 (1952–1973)
Gender (female), % (n) ^a	61.0 (1094)	68.0 (1047)
Characteristics		
Age at Onset (yr), Med (IQR)		26.0 (18.0-38.0)
Duration mean over 10 yrs (%), Med (IQR)		21.0 (6.62-46.5)
Family History (yes), % (n)		75.7 (1165)
Number of DSM symptoms highest ever, Med (IQR)		8.00 (7.00-9.00)
Severity of Symptom (IDS) average score, M (SD)		21.7 (11.6)
Recurring MDD, % (n)	First (no)	29.4 (452)
	Recurrent (yes)	70.0 (1078)
Stage of MDD, % (n)	Stage 2 (1 st episode)	19.7 (303)
	Stage 3 (recurrent episode)	41.0 (631)
	Stage 4 (chronic)	39.3 (605)

IDS=Inventory of Depressive Symptoms; IQR=Inter Quartile Range; M=Mean; MDD=Major Depressive Disorder; Med=Median; n=number; yr=year; SD=Standard Deviation.

^a p-value < .001

Figure 1

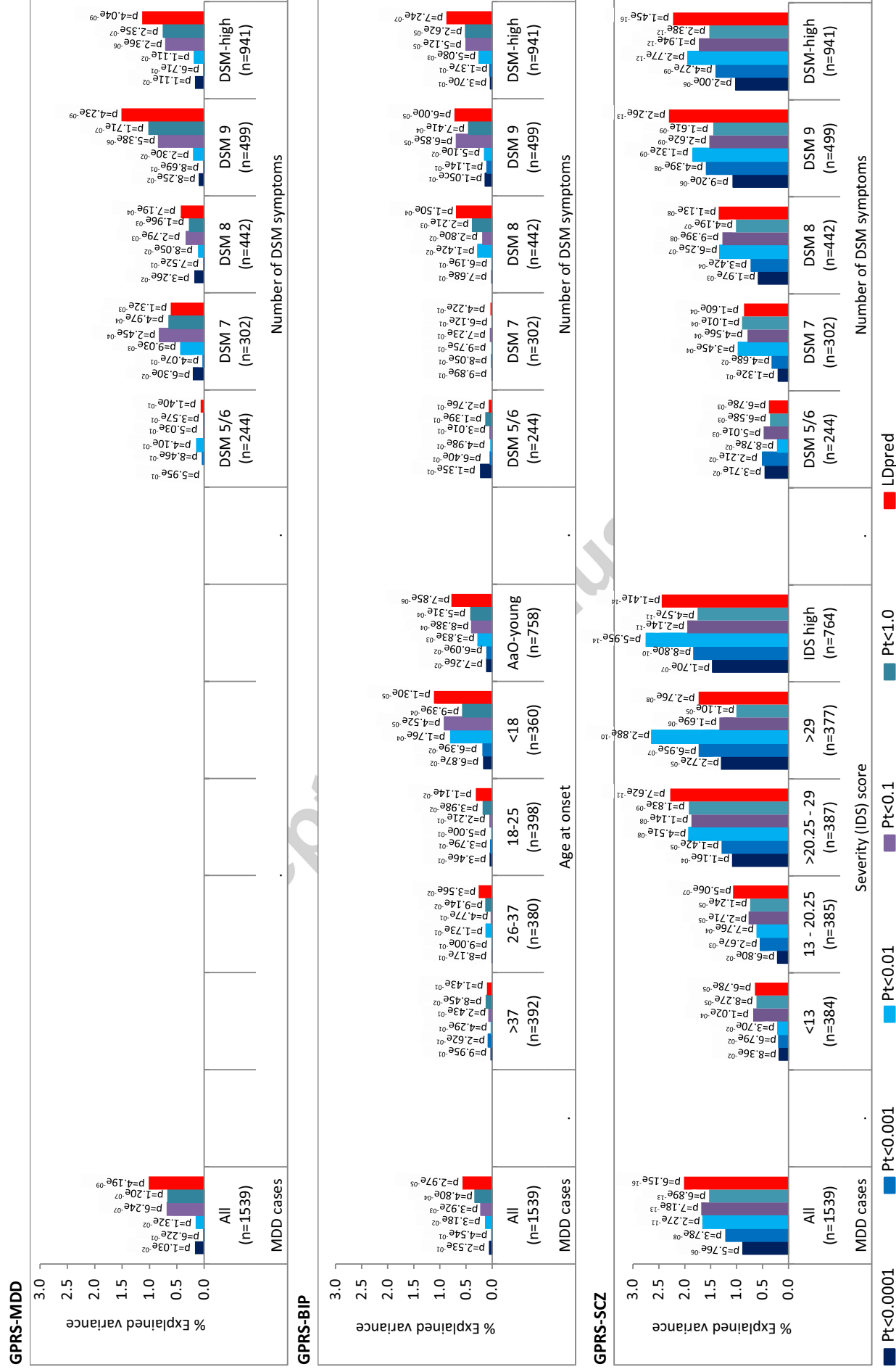


Figure 1

GPRS-SCZ

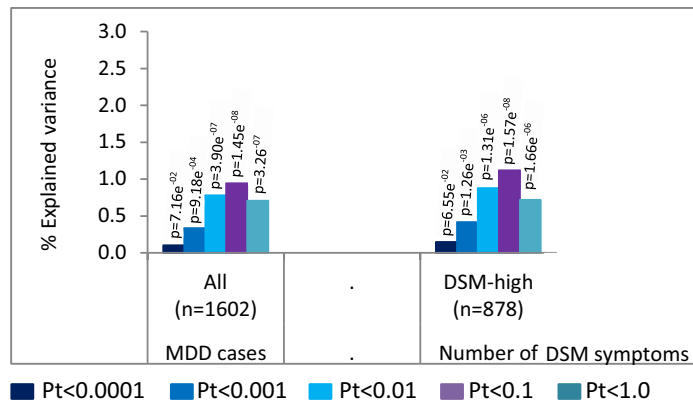


Figure 2

